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Presidential Address

Our Load of Mutations and Its Burden of Disease

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INTRODUCTION

Our favorite subject of human genetics has been much in the limelight this past year, with the birth of the first test tube baby, the claim of the first cloned human, and medical applications of recombinant DNA technology. Each of these developments, real and imaginary, could have consequence not only for the present generation, but, in view of their effects upon selection, for future generations. But their impact upon the ultimately greatest concern of this Society, the human gene pool, seems remote compared to that of another agent much in the news, the chemical mutagen. It is this concern that relates us most strongly to the first presidential address delivered before this Society, nearly 30 years ago, by H. J. Muller.

In that address Muller [1] discussed the principal topic that binds the members of our Society together: our load of mutations. This load is an expression of our genetic variation, it reflects the interplay of mutation and selection in our evolution, and it contributes in ways we are still discovering to our burden of disease. During the interval since Muller's presentation much has been learned about the human gene pool, its interaction with the environment, and its role in disease. In the light of this new knowledge, I would like to look again at our load of mutations and explore some consequences for our Society on the occasion of this meeting.

THE GENETIC LOAD

Although Haldane [2] had previously estimated the mutational and segregational loads nearly equally, Muller chose to emphasize the mutational load, perhaps as an expression of his concern that atomic testing would cause it to be increased seriously. Muller extrapolated from *Drosophila* data to conclude that most of this load could be attributed to mutations with small dominant effect, most of which would be inherited and a few of which would be due to new mutations in any one generation. Because of

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its dominant expression, the total load would then be twice the total mutation rate: $L = 2\Sigma\mu$. The presumed superiority of wild-type alleles has been attributed by Haldane [3] to selection of mutants at other genetic loci that ameliorate any deleterious effect the wild-type allele may have had when it first arose.

Quantitation of the mutational load was attempted by Muller by estimating the number of human genes and their mean rate of mutation to deleterious alleles. He supposed that the gene number for man was 1–2 times the number for *Drosophila* (5,000–10,000 by Muller's estimate) and therefore in the range 5,000–20,000. From data on rates of appearance of new cases of various dominant conditions in man, Muller estimated a mean mutation rate of 2×10^{-5}/locus per generation and concluded that the total mutation rate is probably not less than .1 and not greater than .4. Taking the minimum estimate of .1, and assuming that the average mutation exerts a small deleterious effect, Muller estimated the mutational load to be .20 (i.e., the average individual has a genetic viability that is 80% of an "ideal" individual with no deleterious mutations). He further estimated that the mean detrimental effect of each mutation was 2.5% and the mean number of such mutations per individual was therefore eight.

In the intervening years these estimates have undergone an interesting cycle. When it was discovered that the haploid genetic (DNA) content of human cells was far higher than that of *Drosophila,* the estimate of human gene number was revised upward. Conversely, many investigators concluded that the conditions upon which estimates of mutation rate were based were not representative, and estimates of mean mutation rate were lowered. More recently there has been a return to numbers not very different from Muller's. The remarkably complex organization of the human genome reveals that only a small fraction of the 3 billion nucleotide pairs of man is expressed as translated protein, and that the gene number estimate of 20,000 may be correct. Similarly, the study of mutation rates to functionless alleles, notably by Neel [4, 5], suggests that Muller's mutation rate estimate may also have been correct. Others have made lower estimates of mutation rates in man [6; 7], but gene number may be higher than 20,000, so Muller's conservative estimate of .1 for their product could well be correct (e.g., $2 \times 10^4 \times 5 \times 10^{-6} = .1$).

New data on total mutation rate and mean detrimental effect in *Drosophila* largely substantiate Muller's estimates. In fact, the total mutation rate in this organism seems to be even higher than Muller estimated. Crow [8] concludes that the rate for genes on the second chromosome alone is at least .1. Muller's claim that most mutations have a dominant deleterious effect also seems to be correct. Thus Crow [8] estimates that the average mutant in *Drosophila* decreases heterozygous fitness by 2–3%.

Muller had a great concern that too permissive an attitude would be taken toward radiation and other mutagenic agents, and that the mutational load would be increased to levels incompatible with reproductive compensation. He pointed out that new mutations with small dominant effects would be difficult to detect and warned that follow-up of children of Hiroshima and Nagasaki survivors would probably not reveal a statistically significant effect, even if a real mutational effect had been produced, and so the results would be discounted. This prediction was correct, although, if the observed effects, as on mortality in the children of survivors, are taken at face value,

they are quite consistent with the findings in experimental animals such as the mouse [9]. Moreover, chromosomal damage and a significant induction of cancer have been found in the survivors themselves, so, to the extent that the carcinogenic effect of the radiation has been mediated via mutation in somatic cells, there is support for the concept that germ line mutations were also induced. But now there are biochemical techniques available for assessing subtle mutations, permitting comparison of mutations in irradiated and in unirradiated populations. Meanwhile, mouse studies have been informative regarding doubling doses for mutagenicity. We now speak of doubling doses of the order of magnitude of 25–250 rad for man, and we do not take lightly gonadal exposures of even a few rad in medical or industrial enterprises. Of possibly greater concern now is another hazard Muller mentioned, the myriad of chemicals that assault us. The assessment of these has been frustrating until recently, when the Ames test has stimulated a new hope for evaluation. The genetic effects will of course depend upon the sex of the exposed individual. A special problem in evaluation will be the induction of mutations in fetal oogonial cells by agents that circulate in the pregnant mother. In any case, our society must be aware that the problem of environmental mutagenesis will not go away. On the other hand, the discovery that many mutations are repaired by heritable processes suggests that mutation rate might be manipulated in the opposite direction, and we take great interest in agents that are anti-carcinogenic because they are also anti-mutagenic, in the hope that they might reduce germinal, as well as somatic, mutations.

OUR BURDEN OF CONGENITAL DEFECTS

Muller devoted much of his discussion to the manner in which the genetic load might be expressed, but little was known then for man, and I now wish to review some developments of the intervening years. The total mortality between birth and the end of the reproductive period in nations like the United States and Canada is smaller than Muller's estimate of the genetic load; we are currently not paying for such a load with mortality alone. Another major mode of payment is infertility, which itself takes several forms. Some infertility is secondary to mental or physical disability of genetic origin and has the same effect as postnatal mortality before the end of the reproductive period. Other infertility involves a failure of the early conceptus to survive and is a form of prenatal mortality. Finally there is infertility associated with reproductive failure of various forms. In the genetic contribution to this form of infertility there is no morbidity or mortality. Relaxation of selection against the infertile will of course increase this segment of the load in subsequent generations.

As severe a problem as infertility is for those affected, it is generally considered to be a lighter burden than that of mortality and disability. Although this latter burden is expressed in diverse ways, its most conspicuous component is that of congenital defects. Surely one of the great surprises of the past 30 years was the discovery that chromosomal aberration plays a significant role in human disease. The postnatal incidence of all such abnormalities is approximately 0.5%, nearly all of the cases are lethal before the age of reproduction or are associated with infertility, and virtually all reflect "new" genetic events (i.e., mutations), broadly speaking. Thus the postnatal load of such "new mutations" is approximately .005. This value is about the same as

that obtained for the load of new deleterious dominant mutations that results from a total mutation rate of .1 and a mean deficit of .025 ($2 \times .1 \times .025 = .005$). While this newly discovered chromosomal load of "new mutations" is as large as for new deleterious gene mutations, most chromosomal aberrations are not transmitted to the next generation, so the total postnatal chromosomal load is not much greater than .005.

Muller specifically excluded consideration of the prenatal genetic load, but very little was known about it then. Discovery of chromosomal abnormalities in man led in turn to the discovery that a very large fraction of spontaneous abortuses, currently estimated at 50% or more, is similarly abnormal, so our burden of prenatal mortality has a very large genetic component, even from the point of view of visible chromosomal abnormalities. The absolute amount of prenatal mortality is unknown, but it is at least 20% of all conceptions, and might be much more if early embryonic loss could be assessed. Therefore at least 10% of all conceptuses are chromosomally abnormal. The fact that less than 5% of chromosomally abnormal conceptuses survive to birth indicates that spontaneous abortion is an efficient error-correcting mechanism, even during fetal life, where a striking differential mortality is observed [10]. But the small group of survivors is a major contributor to the postnatal mortality and social burden of congenital defects, so there has been much interest in knowing how to reduce the postnatal incidence of the burden by such measures as counseling older potential mothers, and by employing fetal diagnosis and induced abortion. We may also learn how to improve upon Nature's error-correcting methods by physiological means, leading to what Warkany [11] has called terathanasia. The availability and use of these measures constitute a surprising development since Muller spoke, and will undoubtedly be extended still farther in the future. To the extent that our society decides to do so, we shall pay for this genetic burden at smaller social and even economic cost.

The main burden of prenatal mortality clearly arises genetically. Its non-chromosomal portion may also be largely genetic, but little is known about it. Even in those cases that are not attributable to overt chromosomal aberration, we may expect to find that some are due to small deletions or rearrangements. The analyses of such conditions as retinoblastoma inform us that a particular disorder may be associated with either a deletion, a submicroscopic heritable change, or no germinal change [12]. We therefore cannot quantitate the prenatal genetic load at present. If we assume that for every 100 births there are 20 spontaneous abortions, that 50% of those are chromosomally abnormal, and that the remaining 50% result from dominant gene mutations, then the *prenatal* load from both would be approximately equal to Muller's estimate of 20% for the *postnatal* load of gene mutations. The total genetic load, chromosomal and genic, would be of the order of .4, about .2 prenatal and .2 postnatal (table 1). As noted in the table, the postnatal chromosomal load is relatively small.

Many chromosomal abnormalities can be diagnosed in the fetus, but so can many biochemical defects that are important contributors to *postnatal* mortality and disability. Most of these are recessive disorders that in the past have been lethal, or at least inconsistent with normal fertility. Many other congenital defects cannot yet be diagnosed in the fetus, and many paranatal deaths have not been characterized. We may presume that many more of each will be added to the list of conditions that can be diagnosed in the fetus. To the extent that society is willing to convert this presently

TABLE 1

EXPRESSION OF THE GENETIC LOAD

	Chromosomal	Genic	Total
Prenatal	.1	.1	.2
Postnatal	.005	.2	.2
Total	.1	.3	.4

NOTE.—Fractions are relative to livebirths = 1.00.

paranatal and postnatal mortality to prenatal mortality, we may expect increased utilization of fetal diagnosis and abortion and may someday even consider the possibility that all fetuses should be screened for these abnormalities. Social values are at odds here, with interest in preserving all life on one hand, and alleviating postnatal morbidity and mortality on the other. There are also economic considerations that pit the cost of screening and intervention against the cost of management of these lives. I wish only to emphasize that such programs will not reduce the total prenatal and postnatal genetic load; they only affect the way in which we pay for it.

In fact prenatal intervention can *increase* the size of the recessive genetic load, to the extent that it is followed by compensatory reproduction and increase in heterozygote frequency. This would result in a gradual increase in homozygote frequency with increasing cost to society no matter how this cost is paid. Still this would be a small change and extremely slow in coming. Society has time for thoughtful action, but we should be recording the frequencies of genes we are managing in this way.

Congenital defects will not soon disappear as postnatal problems, so we shall continue to look for new means of managing them, hopefully in definitive ways. So many possibilities of genetic engineering have appeared that could not be imagined 30 years ago, that it is impossible to say where we are headed. Every success is welcome, but we should keep some ledger of costs with and without treatment. In some instances we already know that the economic cost to society is *less* to treat than *not* to treat a defective child. We do not need to panic about the increases in gene and homozygote frequencies that will occur whenever we produce a fertile homozygote; the increases will occur so slowly that we can well afford deliberate action. The relaxed selection that accompanies successful treatment of *dominant* conditions such as retinoblastoma can lead, on the other hand, to rapid increases in gene and disease frequency, in the absence of any selective reproductive control.

If new means for dealing with congenital defects may lead to relaxed selection and increase in the genetic load, the change will be slow. More immediately felt will be the *decrease* in genetic load experienced by efforts to reduce the incidence of dominant and sex-linked disorders. But these disorders would be *increased* by an increase in mutation rate caused by chemical mutagens. These disorders are obviously the ones we should be monitoring so our society can provide a crucial reference point for the future assessment of the new effects of intervention and mutagenesis.

The problems we must face then in the near future with respect to congenital defects

and prenatal mortality are (1) their continuing existence at almost present rates, (2) possibly significant increases in dominant and X-linked semilethal conditions if mutation rates increase, (3) continuing need to deal with chromosomal aberrations, (4) continuing need to treat genetically affected children, and (5) continuing need to deal with the complex of social, economic, and genetic considerations that are involved in developing programs of fetal diagnosis and abortion, population screening, and counseling.

HEREDITY, ENVIRONMENT, AND RELAXED SELECTION

Not all of the genetic congenital defects are maintained in mutational equilibrium, of course, and we are particularly concerned with those that are, or have been, maintained in segregational equilibrium. Both Haldane before Muller and others since have attached more importance to the segregational load than Muller did. Haldane [13] proposed that infectious disease might be a major selective force and in some instances promote an advantage for persons heterozygous for a mutation that is deleterious in the homozygote. He specifically proposed that malaria might have been selective for thalassemia. Muller emphasized the idea that infectious agents, as well as other environmental agents, can be selectively lethal to those with deleterious mutations, and that is in fact why they are deleterious. Selective forces are obviously operating in both directions, and the net genetic effect of the elimination of infectious diseases in early life will depend upon the relative importance of genes that were protective and genes that were predisposing to those infectious diseases.

Chief among the defects thought to have been held in segregational equilibrium are sickle cell anemia, thalassemia, and cystic fibrosis (CF). For these, new mutations are not consequential, and the chief agent of change will be selection. Thus the removal of American blacks from areas of malaria greatly reduced mortality in persons with normal hemoglobin. But even with relaxed selection against the wild-type homozygote, the genetic load from these diseases will be reduced painfully slowly in the absence of intervention. The only method for drastically reducing this burden would be to exert strong selection against heterozygotes that no longer have advantage, as is evidently the case for sickle cell anemia and thalassemia. Taken to its extreme, a selective program could eliminate the offending gene in one generation, but at a large price in reduction of fertility. Such an extreme program might never be socially acceptable, but we should remember that the cost of selection for obsolete polymorphisms must be paid sooner or later. We have a choice between paying it with the morbidity and mortality of homozygote disease, or paying it with screening, counseling, artificial insemination, and prenatal measures (i.e., without postnatal morbidity or mortality).

I would like here to comment on the quantitative assessment of the genetic load of a balanced polymorphism. The genetic load of a balanced polymorphism is commonly measured by the expression $st/s+t$, where s and t are the coefficients of selection for the wild-type and mutant homozygotes, respectively; the heterozygote is considered to have a normal survival value. When selection against the wild-type homozygote is relaxed, the genetic load suddenly decreases, without any change in gene frequency. The decrease is not in the load attributable to the mutant gene but rather a decrease due

to improved survival of the normal homozygote. The calculation also does not take into account the possibility of a slight deleterious effect in the heterozygote. In fact, the genetic load of a mutant allele (a) should take into account only heterozygous (Aa) and mutant homozygous (aa) individuals, not wild-type homozygotes (AA). The illustrative calculations in table 2 are for three situations: selection against AA, relaxation of selection against AA before changes in gene frequencies occur, and relaxation of selection after gene frequencies have changed. In the last situation the load imposed by the heterozygote is greater than that by the homozygote (i.e., the mutant allele would be operating as a mildly deleterious dominant mutation).

For CF, and for some other conditions, we need to know whether the presumed heterozygote advantage is still operating, and if so, what its basis may be. It is even conceivable that the frequency of the CF gene (or genes) is still increasing. Fortunately, at least in the United States population, we do not have many identifiable recessively lethal conditions with heterozygote frequencies greater than 1%, but virtually nothing is known about the survival values of heterozygotes for conditions with homozygote frequencies less than one per 10,000. The genetic load imposed by 100 recessively lethal conditions, each with a frequency of one per 10,000, would be only .01. The necessary heterozygote advantage for equilibrium for such a condition would only be 1%, and virtually impossible to identify in American populations. It therefore seems that our efforts to reduce mortality from recessively lethal genes in segregational equilibrium should be confined to just a few disorders.

The resistance that hemoglobinopathy genes may offer against malaria serves to remind us that the burden of *infectious disease* falls unequally upon our population. By

TABLE 2

GENETIC LOAD ATTRIBUTABLE TO A HYPOTHETICAL ALLELE WITH BALANCED POLYMORPHISM AND AFTER RELAXATION OF SELECTION AGAINST WILD-TYPE HOMOZYGOTE

	WITH BALANCED POLYMORPHISM	WITH RELAXED SELECTION	
		Immediately	Much later
Allele frequency:			
A	.95	.95	.99
a	.05	.05	.01
Genotype frequency:			
AA	.90	.90	.98
Aa	.095	.095	.02
aa	.0025	.0025	.0001
Selection coefficient:			
AA	.05	.00	.00
Aa	.01	.01	.01
aa	1.00	1.00	1.00
Load on AA	.045	.00	.00
Genetic load:			
Aa	.00095	.00095	.0002
aa	.0025	.0025	.0001
Total	.0035	.0035	.0003
Total load	.049	.0035	.0003

TABLE 3

UNITED STATES MORTALITY IN AGES 1–4/100,000

	1940	1950	1975
Tuberculosis	12	6	0.1
Pneumonia	63	19	4
Enteritis	72	13	1
Appendicitis	8	1	0.1
Accidents	48	37	28
Malformations	10	11	9
Cancer	5	12	6
All causes	290	139	71

NOTE.—Data obtained from [15] and table 63 in [14].

genetic predisposition some individuals are particularly susceptible. This kind of genetic variation may explain the early susceptibility of American Indian populations to smallpox and of Polynesian populations to measles. Such a genetic difference may explain the development of severe infection in only some individuals who carry such a potentially virulent organism as meningococcus, or of paralysis in only some persons who are infected with the poliomyelitis virus. Now what is the effect of preventing or curing many of these infections, as has happened for much of pneumonia, enteritis, tuberculosis, poliomyelitis, and numerous other infectious conditions? On the one hand, some individuals may have been genetically protected, and, on the other hand, some may have been genetically endangered. Muller preferred to think that the net effect of relaxed selection was to favor the genetically enfeebled. We are now more cautious about evaluating the balance of good and bad. Certainly it is difficult to conclude that elimination of a disease like malaria will *weaken* the species genetically.

The relaxed selection that was already occurring for infectious diseases before Muller, has continued since and is little short of dramatic. Consider, for example, the changes in mortality that have occurred in children aged 1–4 in the United States (table 3). A sharp decline occurred for infectious diseases, following an earlier decrease in conditions such as diphtheria and whooping cough. Now, however, we are continuing to be faced with mortality due to accidents, malformations, and cancer. The earlier increase in cancer is primarily attributable to improved diagnosis, whereas the later decline represents improved cure rates in this age group. To the extent that these causes of death are genetically determined, there has been a substantial decrease in the expression of the genetic load in the form of mortality. It is certainly true that genetic predisposition plays a role in malformations and cancer, but it is not clear that this is important for accidents. Muller was concerned that society would be paying a high price for this preservation of life, but this is probably not true for this young age group; there has been a decrease in mortality for infections, and there are fewer pediatric beds per capita now than in 1950.

Relaxed selection is noted for older age groups as well. Thus a similar trend is noted for persons around the age of 30, approximately the average age for parenting in the

TABLE 4

UNITED STATES MORTALITY IN AGES 25–34/100,000

	1940	1950	1975
Tuberculosis	56	19	0.3
Pneumonia	17	4	3
Appendicitis	7	1	0.1
Pregnancy	18	5	0.5
Accidents, suicide, and homicide	78	65	80
Cardiovascular	41	31	13
Cancer	17	20	15
All causes	306	179	143

NOTE.—Data obtained from [15] and table 63 in [14].

United States (table 4). Here the refractory causes of death are cancer, heart disease, and the complex of accidents, murder, and suicide. The genetic component of this burden of disease may also be significant because of known genetic predisposition to hypertension, myocardial infarction, and cancer, especially at earlier than usual age. For later age, about 60 years, the genetic component is still present, but its contribution to expressed genetic load is smaller or nonexistent because it is paid beyond the reproductive period (table 5). Note the decreasing cardiovascular mortality, due to decreased incidence and improved early treatment, and the increasing lung cancer mortality, attributable to cigarette smoking, possibly associated with a genetic predisposition.

PAYMENT OF THE POSTNATAL LOAD

Now when one assesses the total expressed mortality over the postnatal life span, it is clear that the majority of people in the United States, 81.8%, survive to 60 years, or

TABLE 5

UNITED STATES MORTALITY IN AGES 55–64/100,000

	1940	1950	1975
Tuberculosis	76	47	4
Pneumonia	98	38	27
Appendicitis	17	4	0.7
Accidents, suicide, and homicide	140	102	77
Cardiovascular	1122	1068	684
Cancer			
Respiratory	46	94	132
Other	322	297	299
All causes	2516	1901	1496

NOTE.—Data obtained from [15] and table 63 in [14].

TABLE 6

SURVIVAL IN THE UNITED STATES

Age (years)	1950	1975
Birth	100.0%	100.0%
1	97.0	98.4
10	96.2	97.9
20	95.4	97.3
30	93.9	95.9
40	91.7	94.2
50	86.6	90.4
60	75.9	81.8
70	57.0	65.5
80	29.3	39.0

NOTE.—Data obtained from [16] and table 49 in [14].

two generation times (table 6, fig. 1). Even if most of the postnatal mortality in the United States by the age of 40 is associated with deleterious genes, the postnatal genetic load paid by mortality would be approximately .05; if there is a postnatal genetic load as great as .20, only one quarter of it is being paid for with mortality. Of

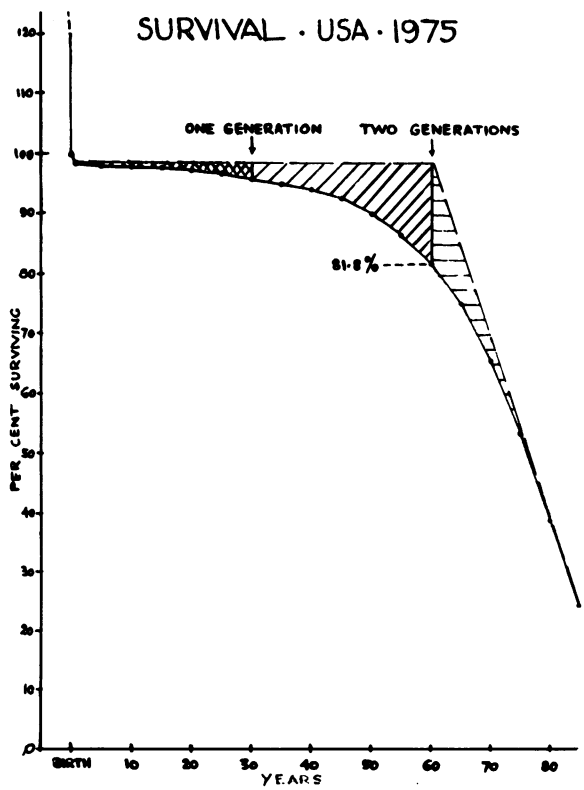

FIG. 1.—The prospects for survival in the United States, 1975. Data from table 6.

course payment is made by infertility as well as mortality. As noted earlier, some infertility is associated with morbidity, if not mortality, and is very burdensome to society. Other infertility is primary, and is more indirectly burdensome. These two forms of infertility together must be more substantial than mortality as modes of payment, should the total postnatal genetic load be as great as .20.

Some of the secondary infertility we now experience is of recent origin, following the decrease in mortality from infectious diseases. To illustrate this shift of mortality to secondary infertility, consider the reduction in mortality from two causes, pneumonia and enteritis. In 1940 the combined mortality for these two diseases in the first year of life was 1.1%, and in 1975 just 0.1%. Some of this mortality was associated with a genetic disorder, CF of the pancreas, a disease for which selection has been relaxed. The incidence of this disease is approximately one per 2000 births, or 0.05%. From this we can deduce that CF could have accounted for as much as 5% of the mortality from pneumonia and enteritis in 1940. Although the mortality of CF has diminished, its morbidity and cost to society remain high. It is still largely a lethal disorder genetically, since the fertility of survivors is greatly reduced.

CF presents an unusual situation in that it is a relatively common lethal genetic disorder. But, as Muller pointed out, many genes salvaged by modern medicine may have small deleterious effects expressed via morbidity or mortality later in life, often after reproduction, and escape selection. Muller's concern was that the gene pool would therefore steadily deteriorate. But we have seen that selection can also reduce deleterious genotypes, as with sickle cell anemia, and perhaps even CF. Quantitative assessment of the fraction of the genetic load currently paid by infertility secondary to deleterious genes is not possible, but in table 7 this fraction is made equal to that of postnatal mortality. The remainder of the load is attributed to primary infertility, although again, this cannot yet be estimated accurately.

Although much has been learned about genetic factors in prenatal mortality and postnatal morbidity and mortality, little is known about genetic factors in primary infertility. Yet they are obviously important if the genetic load attributable to primary infertility approaches 10%. This load is of the same magnitude as those estimated here for prenatal and for postnatal gene loads. If we naively assume that genetic load reflects gene number, then approximately equal numbers of our genes seem to be necessary for germ cell production and fertilization, for embryogenesis, and for subsequent physiological activity.

As noted earlier, Muller expressed alarm that this payment of mortality and

TABLE 7

PAYMENT OF THE POSTNATAL LOAD

Payment	
Mortality	.05
Infertility secondary to morbidity	.05
Primary infertility	.10
Total	.20

infertility for our load of mutations may be approaching the limit for the species, and that a significant increase in our load would outstrip our reproductive potential. I suppose many of us find this difficult to believe in a world concerned about the population explosion. On the other hand, many countries have experienced a marked slowing in population growth, and do seem to be approaching a steady state. Much of this is being achieved by a high rate of induced abortion, a fact hardly foreseeable 30 years ago. A steady state achieved with a significant induced abortion rate suggests that some increment of reproductive increase is still possible.

THE FUTURE

We see, then, that the populations of nations like Canada and the United States bear a genetic load that is currently expressed via a heavy prenatal and neonatal mortality, a vastly smaller postnatal mortality, and some as yet undetermined partition of secondary and primary infertility. This load can only be *increased* by germinal mutations, and although our society is taking steps to reduce this hazard, we must continually remember the consequences of *not* doing so. We almost certainly have enough genetic variation for purposes of evolution. The price of evolution is some fraction of genetic "eliminations," so our awareness of the importance of the individual is heightened, even in this era of talk about a "cloned man." Our society seems to be moving toward a goal of averting genetic disaster when possible, and accomplishing these genetic eliminations via selective infertility and prenatal mortality rather than postnatal mortality and morbidity. For those who *are* born with a genetic handicap, increasing attention is being given to the alleviation of their suffering, and the world of molecular biology can be expected only to step up the pace of this effort. We now consider the possibility of identifying genetic predisposition to acquired disease early in life and expending great effort toward the end that all of us shall survive to old age.

These efforts are on the pathway toward which Muller was directing us at the birth of this Society. Indeed, Muller not only warned against increasing mutation rates and advocated selective reproduction, but he also urged the betterment of man's intellect and social behavior by genetic means. For the near future we shall probably be spending most of our energy on the first two efforts, largely with methodologies for the assessment of mutagens, and for selective genetic elimination that were then unknown. These efforts themselves have raised such broad social issues that it is difficult to imagine an early serious encounter with the last of Muller's recommendations.

I have used the expression "our Society" in this talk, and I would like to call attention to the fact that it is our American Society of Human Genetics more than any other segment of our larger society that must think about our genetic load and its management. Our Society recognizes the inevitability of a genetic load in an evolving organism and of the burden of disease it brings if no effort is made to deal with it. The members of our Society, more than any other, have the understanding and skills required to reduce that burden of disease by utilizing less tragic ways to pay for the genetic load. Every segment of our Society is essential, whether its members be concerned with large populations or with individual phenotypes. I hope that in our annual meetings and in our Journal we keep this in mind and make a sustained effort to promote the exchange of ideas and to avoid the isolation that can accompany

specialization. Ours is the one Society bound together by our genetic load, its burden of disease, and the present means for dealing with them.

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